REMARKS/ARGUMENTS

I. STATUS OF THE CLAIMS

Upon entry of this amendment, claims 1-66 are pending in this application and are presented for examination. Claims 19 and 20 are amended herein to correct typographical errors made without deceptive intent. No new matter has been introduced with this amendment. Reconsideration is respectfully requested.

II. REJECTIONS UNDER 35 U.S.C. §102(a)

The claims have been rejected in various combinations under 35 U.S.C. § 102(a) over a number of different references. Each of these rejections is traversed in detail below.

For a rejection of claims under § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference... There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

A. First Rejection Under 35 U.S.C. §102(a)

Claims 1-8, 12-13, 15-17, 21-22, 32-39, 43-45, 49, 55, 57, and 59 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Lee *et al.* (U.S. Patent No. 5,908,777) ("Lee *et al.* 1"). Applicants respectfully traverse the rejection.

The Examiner alleges that Lee *et al.* I discloses compositions containing a condensed nucleic acid encapsulated within a liposome (*see,* Office Action at page 2). In

response, Applicants assert that Lee *et al.* 1 fails to teach all of the elements of the claimed invention.

As explained by Dr. Ian MacLachlan in his Declaration under 37 C.F.R. §1.132 submitted herewith, Lee *et al.* I discloses nucleic acid-lipid ***complexes*** comprising anionic liposomes and nucleic acid-polylysine complexes formed by mixing preformed liposomes with nucleic acid-polylysine complexes in deionized water (*see,* Declaration at paragraph 9). As Dr. MacLachlan clarifies, given that DNA does not readily cross lipid membranes, one of skill in the art would appreciate that mixing a nucleic acid-polylysine complex with preformed liposomes in an aqueous solution does not result in entrapment of DNA within the internal space of the liposomes, but would, instead, result in the formation of nucleic acid-lipid ***complexes*** (*see,* Declaration at paragraph 9).

In response to the Examiner's concern that these arguments are merely speculative, Dr. MacLachan has supervised an additional experiment that demonstrates this is indeed the case. In this experiment, pre-condensed DNA was mixed with preformed liposomes in deionized water according to the teachings of Lee *et al.* The result of the experiment was that only 2.5% of the DNA was rendered inaccessible to the Picogreen probe (*see,* Declaration at paragraph 13 and Exhibit B). This is in stark contrast to the liposomal encapsulation of pre-condensed DNA resulting from the use of the method taught in the current specification. When the current method was used, 41% of the pre-condensed DNA was rendered inaccessible to the Picogreen probe (*see,* Declaration at paragraph 13 and Exhibit B). In his Declaration, Dr. MacLachlan states that the 2.5% DNA that was rendered inaccessible by the methods of Lee *et al.,* and that it:

> [I]s ***not liposomally encapsulated***, but rather exists in a state as shown in the third step of Figure 1 of Lee *et al.* This state consists of an intact liposome wrapping its ***exterior*** around the DNA/Polycation complex, as illustrated with the 'Pacman'-like cartoon. In this state, the DNA is less accessible to the Picogreen than when free in solution, resulting in the reduced signal generated in the experiments described below. (*see,* Declaration at paragraph 10)

The Examiner has also alleged that Figure 1 of Lee *et al.* clearly shows the encapsulation of the complex. In response, Applicants respectfully assert that this is not the case. As explained by Dr. MacLachlan in his Declaration, Figure 1 of Lee *et al.* does not properly illustrate the results of the methods taught in the specification. As evidenced by the experiments described at paragraph 13 of this declaration, the methods of Lee *et al.* ***do not*** result in the liposomal encapsulation of DNA (*see,* Declaration at paragraph 10). Further, it is Dr. MacLachlan's expert scientific opinion that the resulting cartoon representation of the alleged encapsulated DNA is in fact a representation of the alleged encapsulation of ***non-complexed*** DNA (*see,* Declaration at paragraph 10). As Figure 1 actually shows the encapsulation of non-complexed DNA, Applicants respectfully submit that Figure 1 of Lee *et al.* does not teach the liposomal encapsulation of a condensing agent-nucleic acid complex as set forth in the pending claims.

Thus, in contrast to the presently claimed liposomes, the nucleic acid-lipid ***complexes*** of Lee *et al.* 1 do ***not*** comprise a nucleic acid fully encapsulated in a liposome (*see,* Declaration at paragraphs 9, 10, and 18). Accordingly, Lee *et al.* 1 does not anticipate the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw this aspect of the rejection under 35 U.S.C. § 102(a).

B. Second Rejection Under 35 U.S.C. §102(a)

Claims 1-6, 8, 12-13, 15-17, 21-22, 28, 32-37, 39, 43-45, 49, 55, 57, and 59 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Martin *et al.* (U.S. Patent No. 5,891,468). Applicants respectfully traverse the rejection.

The Examiner alleges that Martin *et al.* disclose compositions containing condensed nucleic acid preparations encapsulated within a liposome (*see,* Office Action at page 4). In response, Applicants assert that Martin *et al.* fails to teach all of the elements of the claimed invention.

As explained by Dr. MacLachlan in his Declaration under 37 C.F.R. §1.132 submitted herewith, Martin *et al.* discloses ***complexes*** formed by mixing preformed liposomes with plasmid-histone complexes (*see,* Declaration at paragraph 11). Thus, as Dr. MacLachlan

has clarified, Martin *et al.* does not describe nucleic acid-histone complexes fully encapsulated in a liposome (*see,* Declaration at paragraph 11).

Dr. MacLachlan further clarifies that the dehydration-rehydration-extrusion methods described in Martin *et al.* cannot be used to encapsulate nucleic acids (*see,* Declaration at paragraphs 10 and 13). Specifically, Dr. MacLachlan describes experiments conducted under his supervision that use dehydration-rehydration-extrusion methods to attempt to encapsulate condensing agent-nucleic acid complexes in liposomes (*see,* Declaration at paragraph 13).

The results from the experiments are set forth in Exhibit B accompanying the Declaration and demonstrate that condensing agent-nucleic acid complex encapsulation is not accomplished by using the method taught in Martin *et al.* Specifically, Dr. MacLachlan did not see any incorporation of the polyplex by this method as all of the DNA was accessible to the Picogreen probe. Therefore, these results unequivocally demonstrate that the dehydration-rehydration-extrusion methods set forth in Martin *et al.* do ***not*** produce liposomes that encapsulate condensing agent-nucleic acid complexes (*see*, Declaration at paragraphs 11, 13, and 18). Thus, Martin *et al.* does not anticipate the presently claimed liposomes encapsulating a nucleic acid-condensing agent complex.

In view of the foregoing remarks, Applicants respectfully request the Examiner to reconsider and withdraw this aspect of the rejection under 35 U.S.C. § 102(a).

C. Third Rejection Under 35 U.S.C. §102(a)

Claims 1-8, 12-13, 15-17, 21-22, 32-39, 43-45, 49, 55, 57, and 59 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Lee *et al.* (*J. Biol. Chem.*, 271:8481-8487 (1996)) ("Lee *et al.* 2"). Applicants respectfully traverse.

The Examiner alleges that Lee *et al.* 2 discloses compositions containing a condensed nucleic acid encapsulated within a liposome (*see,* Office Action at page 5). In response, Applicants assert that Lee *et al.* 2 fails to teach all of the elements of the claimed invention.

As explained by Dr. Ian MacLachlan in his Declaration under 37 C.F.R. §1.132 submitted herewith, Lee *et al.* 2 discloses nucleic acid-liposome ***complexes*** that are the same as or similar to the complexes disclosed in Lee *et al.* 1 (*see*, Declaration at paragraph 12).

Specifically, Lee *et al.* 2 describes lipoplexes, *i.e.*, ***complexes*** between the liposomes and nucleic acid-condensing agent which are formed by mixing preformed anionic liposomes with nucleic acid-polylysine complexes in deionized water (*see,* Declaration at paragraph 12). As discussed above in connection with the anticipation rejection of Lee *et al.* I and as explained by Dr. MacLachlan, one of skill in the art would appreciate that mixing preformed liposomes with nucleic acid-polylysine complexes in an aqueous solution would result in the formation of lipoplexes, and ***not*** liposomes fully encapsulating a nucleic acid (*see,* Declaration at paragraph 12). As also discussed above, the experiments supervised by Dr. MacLachlan further evidence that the method disclosed by Lee *et al.* 2 ***does not*** result in the liposomal encapsulation of condensing agent-nucleic acid complexes (*see*, Declaration at paragraph 13 and Exhibit B). Thus, in contrast to the presently claimed liposomes, the nucleic acid-lipid complexes of Lee *et al.* 2 also do not comprise a condensing agent-nucleic acid complex fully encapsulated in a liposome. Accordingly, Lee *et al.* 2 does not anticipate the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request the Examiner to reconsider and withdraw this aspect of the rejection under 35 U.S.C. § 102(a).

III. REJECTIONS UNDER 35 U.S.C. §103(a)

The claims have been rejected in various combinations under 35 U.S.C. § 103(a) over a number of different references. Each of these rejections is traversed in detail below. To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. MPEP § 2143. *See also*, *In re Rouffet,* 47 USPQ2d 1453 (Fed. Cir. 1998). The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

A. First Rejection Under 35 U.S.C. §103(a)

Claims 11-14, 26-28, 30-31, 42, 52-53, 56, 58, and 62-63 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lee *et al.* 1 or Lee *et al.* 2. Applicants respectfully traverse the rejection.

In making this rejection, the Examiner acknowledges that neither Lee *et al.* I nor Lee *et a l.* 2 teaches or suggests diameters of the condensing agent-nucleic acid complex, the claimed lipid:nucleic acid ratios, or the addition of the condensing agent in stages or the addition of two condensing agents, but concludes that each of these parameters would be obvious in view of Lee *et al.* 1 or Lee *et al.* 2 (*see,* Office Action at pages 6-7). However, as discussed above in connection with the §102(a) rejections and as explained by Dr. MacLachlan in his Declaration, neither Lee *et al.* 1 nor Lee *et al.* 2 discloses or even suggests the presently claimed liposomes encapsulating a nucleic acid-condensing agent complex (*see*, Declaration at paragraphs 9, 10, 12, and 18).

Further, the experiments supervised by Dr. MacLachlan, as discussed above and in the Declaration at paragraph 13, clearly demonstrate that the methods employed by Lee *et al.* 1 and 2 ***do not*** result in the liposomal encapsulation of condensing agent-nucleic acid complexes as set forth in the currently pending claims. Absent such a teaching or suggestion, the compositions and methods of the presently claimed invention are nonobvious, and thus patentable over Lee *et al.* 1 or Lee *et al.* 2. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

B. Second Rejection Under 35 U.S.C. §103(a)

Claims 17-22, 28-29, 45-48, 53-54, 60, and 63-64 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* in view of Holland *et al.* (U.S. Patent No. 5,885,613). Applicants respectfully traverse the rejection.

In making this rejection, the Examiner acknowledges that none of Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* discloses PEG-ceramide, but cites Holland *et al.* as disclosing liposomal formulations comprising PEG-ceramide, and concludes that the presently claimed liposomal compositions would have been obvious over Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* in view of Holland *et al.* (*see,* Office Action at pages 7-8).

As discussed in detail above and as explained by Dr. MacLachlan, the presently claimed invention is directed to compositions comprising a nucleic-acid-condensing agent complex ***encapsulated*** in a liposome (*see*, Declaration at paragraph 7). In contrast to the presently claimed invention, Lee *et al.* 1, Lee *et al.* 2, and Martin *et al.* each disclose nucleic-acid lipid ***complexes*** (*see*, arguments above and Declaration at paragraphs 9, 11 and 12). The disclosure of Holland *et al.* of PEG-ceramide does not remedy the defect in each of these references. As explained by Dr. MacLachlan, Holland *et al.* discloses the use of PEG-ceramide in a nucleic acid lipid ***complex*** (*see*, Declaration at paragraph 15). More particularly, Holland *et al.* states:

> Cationic lipids have been used in the transfection of cells in vitro and in vivo. . . .The efficiency of this transfection has often been less than desired, for various reasons. ***One is the tendency for cationic lipids complexed to nucleic acid to form unsatisfactory carriers. These carriers are improved by the inclusion of PEG lipids.***
> *See,* column 12, lines 28-39 of Holland *et al.* (emphasis added).

Thus, the teachings of Holland *et al.* are clearly directed to forming nucleic acid-cationic liposome ***complexes***, which are structurally and functionally different from the presently claimed liposomes, wherein the nucleic acid-condensing agent complex is encapsulated in the liposome and is resistant in aqueous solution to degradation with a nuclease (*see*, Declaration at paragraph 15). Thus, the cited references, alone or in combination, do not teach or suggest the presently claimed liposomes ***encapsulating*** a condensing agent-nucleic acid complex. Absent such a teaching or suggestion, the compositions and methods of the presently claimed invention are nonobvious, and thus patentable over Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* in view of Holland *et al.* Accordingly, Applicants respectfully request the reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

C. Third Rejection Under 35 U.S.C. §103(a)

Claims 8-10, 23-25, 39-40, 50-51, and 61 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* in view of Lisziewicz *et al.* (U.S. Patent No. 6,420,176). Applicants respectfully traverse the rejection.

In making this rejection, the Examiner acknowledges that none of Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* discloses the use of polythethylenimine, but cites Lisziewicz *et al.* as disclosing polyethylenimine as a nucleic acid condensing agent, and concludes that the presently claimed liposomal compositions would have been obvious over Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* in view of Lisziewicz *et al.* (*see,* Office Action at page 9).

As discussed in detail above and as explained by Dr. MacLachlan, the presently claimed invention is directed to compositions comprising a nucleic-acid-condensing agent complex encapsulated in a liposome (see, Declaration at paragraph 7). In contrast to the presently claimed invention, Lee *et al.* 1, Lee *et al.* 2, and Martin *et al.* each disclose nucleic-acid lipid complexes (*see*, arguments above and Declaration at paragraphs 9, 11 and 12). As explained by Dr. MacLachlan, the disclosure of Lisziewicz *et al.* of polyethylenimine (PEI) does not remedy the defect in any of these references (*see*, Declaration at paragraph 16). If anything, Lisziewicz *et al.* teaches away from the use of PEI. Specifically, as Dr. MacLachlan clarifies, Lisziewicz *et al.* compares the efficiency and toxicity of PEI and PEI-mannose as a condensing agent and demonstrates that relative to PEI mannose, PEI (1) is more toxic; (2) requires more DNA to neutralize; and (3) is less efficient for transfection (*see*, Declaration at paragraph 16). Thus, one of skill in the art would not have been motivated to use PEI in view of the disclosure of Lisziewicz *et al.* Even if Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* were combined with Lisziewicz *et al.*, the combination would not lead to the presently claimed invention because none of the cited references, alone or in combination, teaches or suggests condensing agent-nucleic acid complexes ***encapsulated*** in a liposome. Absent such a teaching or suggestion, the compositions and methods of the presently claimed invention are nonobvious, and thus patentable over Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* in view of Lisziewicz *et al.*

Accordingly, Applicants respectfully request the reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

D. Forth Rejection Under 35 U.S.C. §103(a)

Claims 65-66 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* in combination with Papahadjopoulos *et al.* (WO 98/20857). Applicants respectfully traverse the rejection.

In making this rejection, the Examiner acknowledges that none of Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* discloses the use of reverse phase evaporation or detergent dialysis to prepare liposomes, but alleges that Papahadjopoulos *et al.* describes such methods for making liposomes (*see,* Office Action at page 10).

As discussed in detail above and as explained by Dr. MacLachlan, the presently claimed invention is directed to compositions comprising a nucleic-acid-condensing agent complex ***encapsulated*** in a liposome (*see*, Declaration at paragraph 7). In contrast to the presently claimed invention, Lee *et al.* 1, Lee *et al.* 2, and Martin *et al.* each disclose nucleic-acid lipid ***complexes*** (*see*, arguments above and Declaration at paragraphs 9, 11 and 12). Moreover, as explained by Dr. MacLachlan, Papahadjopoulos *et al.* does not remedy the defect in any of these references (*see*, Declaration at paragraph 17). Papahadjopoulos *et al.* discloses nucleic acid-lipid ***complexes*** formed by mixing preformed liposomes with nucleic acids, which leads to the formation of lipoplexes, *i.e.*, complexes between the nucleic acids and liposomes, but will ***not*** lead to encapsulation of the nucleic acid in the liposomes (*see*, Declaration paragraphs 9 and 17). In fact, the disclosure of Papahadjopoulos *et al.* explicitly states that the methods described therein are used for forming ***complexes*** between preformed liposomes and nucleic acids and does not disclose or suggest encapsulating nucleic acids in liposomes using detergent dialysis or reverse phase evaporation (*see*, Declaration at paragraph 17). Thus, the cited references, alone or in combination, do not teach or suggest condensing agent-nucleic acid complex ***encapsulated*** in a liposome. Absent such a teaching or suggestion, the compositions and methods of the presently claimed invention are nonobvious, and thus patentable over Lee *et al.* 1, Lee *et al.* 2, or Martin *et al.* in combination with Papahadjopoulos *et al.*

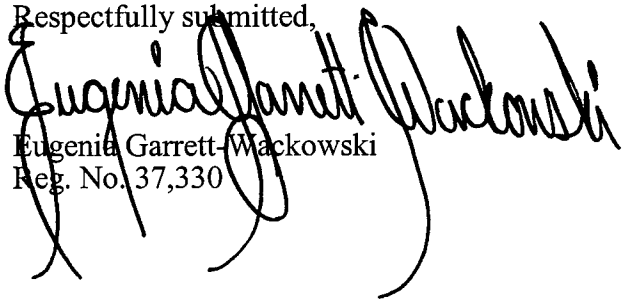
Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Eugenia Garrett-Wackowski
Reg. No. 37,330

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
EGW:aja
61328345 v1